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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/580,542	03/02/2007	David Wallach	WALLACH34	3237

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EXAMINER	
STOICA, ELLY GERALD	

ART UNIT	PAPER NUMBER
1647	

MAIL DATE	DELIVERY MODE
09/28/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/580,542	WALLACH ET AL.	
	Examiner	Art Unit	
	ELLY-GERALD STOICA	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-58* is/are pending in the application.

4a) Of the above claim(s) *26-58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 July 2009* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. In the amendment filed on 07/22/2009 Applicant amended claims 21 and 22. Claims 21-58 are pending and claims 26-58 remain withdrawn for the reasons of record. Claims 21-25 are currently examined.

Withdrawn objections

2. The objection to the drawings 2c, 3i and 4b are withdrawn since the corrections are accepted by the Examiner.

3. The objections to the claims are withdrawn in view of the amendments to the claims.

Maintained Claim rejections

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 21-25 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for the reasons of record. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

As iterated in the previous office action, the prior art does not show interaction between NIK and SIVA and a link between this interaction and any disease.

While the level of skill in the art of in vitro inhibiting interaction between intracellular proteins is high, the relative skill to inhibit such interaction in living organisms is low, especially in the absence of any disease or condition to be treated. That is because the predictability of the in vivo methods for successfully delivering agents that would modulate the interaction between two intracellular proteins is extremely **low.** In this respect, a skilled artisan would have to introduce in a living organism (i.e. not in cell culture) antibodies (or another modulator of proteic or nucleic acid nature) that might potentially block the interaction by binding to any of the interacting partners or nucleic acids that would block translation of RNA in to the proteins of interest. None of these procedures have been successfully used to treat any disease *in vivo* and serious hurdles would have to be considered (Richardson et al, Gene therapy, 5, 635-644, 1998; Lo et al. Handb. Exp Pharmacol. 181, 343-373, 2008). Also the procedures need to be directed to specific cells since a generalized administration of the agent to all the cells of the body, given the centrality of the NIK in signaling pathways in normal cells, would potentially represent a harmful situation for the organism. All the procedures would have been performed without the certitude that the interaction between NIK-SIVA is linked to any disease and without the data showing that such a modulation of the interaction would constitute efficient treatment. The guidance provided in the specification is at best at the level of hypothesis to be tested and not as guidance to use a method with likely success. The specification for instance

mentions (p. 21, lines 27-30) that upregulation of SIVA-CD27 signaling would overcome myelogenesis. However, this is an untested hypothesis since Katayama et al. (Br J Haematol. 120, 223-234, 2003) states that they were unable to determine if the SIVA protein is pro-apoptotic protein. The language of the specification is highly speculative, providing just a working hypothesis with uncertain outcomes For instance, even of the "working examples", example 6, titled "SPECULATIVE MODEL OF THE MECHANISMS INITIATING NF-κ B ACTIVATION BY TNF AND CD 70" presents no actual working example to verify the model, let alone link it to a method of treatment of a disease. Thus, the teachings set forth in the specification provided no more than a "plan" or "invitation" for those of skill in the art to experiment. It is considered that the amount of experimentation to determine a causative link between NIK-SIVA interaction and a disease and then the treatment of this disease would be enormous, given the hurdles of delivering an agent to the cells intended as recipients (Wendtner et al. Leukemia & Lymphoma, 45, 897-904, 2008).

Also, there are no working models for the treatment of any immune disorder by modulation of the NIK-SIVA interaction, either in the specification or in the prior art.

Due to the large quantity of experimentation necessary to uncover the diseases in which NIK-SIVA interactions are certainly and causatively implicated and then to successfully test therapeutic procedures; the lack of direction/guidance presented in the specification regarding successful methods of treatment; the absence of working examples directed to same; the complex nature of the invention; the state of the prior art which establishes the unpredictability of treating diseases linked to intracellular protein-

protein interaction *in vivo*; and the unpredictability of the link of NIK-SIVA interactions to any disease, undue experimentation would be required of the skilled artisan to use the claimed invention in its full scope.

6. On page 16-18 of the Remarks Applicant argues the specification demonstrates a causative link between NIK-SIVA interaction and a disease by citing paragraph from the specification. The arguments were carefully considered but not found persuasive because the paragraphs cited ([0001], [0008], [0012], and [0093]) describe, in the best case scenario, the potential involvement of BLys in immune disorders such as (B-CLL). There is no indication of interaction between NIK and SIVA and the effect that a modulation of this interaction has on proteins like BLys. Since the invention refers to a method of treatment by modulating the NIK-SIVA interaction the arguments presented by Applicant on pages 16-18 are not pertinent to the rejection. Moreover, the citation on page 18 of the therapeutic application of the invention is based on speculative a mechanism the "envisages down regulation of BLys signaling through NIK-dependent NF-kB pathway to overcome the described immune disorders." There is no proof of NIK-SIVA interaction and how modulation of it would affect other proteins in the cell. Further, on page 19, Applicant alleges that the specification establishes a "link/mechanism" by which the claimed method can modulate the NIK-SIVA complex. Again, there are no facts present but an unproven hypothesis. This listing of diseases in paragraph [0012] constitutes a mere invitation to experiment, as there is no data or reason to expect that those specific diseases would be treatable by the method of the invention, and hence is not enabling. Also the alleged link between NIK and BLys in multiple myeloma,

discussed in the [0093] of the specification, is not addressing the elected invention, since it does not address the NIK-SIVA interaction.. all that is shown is that BLys is "associated" with the diseases. Discovery of the active agent(s) would require undue experimentation, and is merely an invitation to experiment to find such. Association is neither causality, nor a sufficiently predictable treatment plan.

7. On page 18 of the Remarks Applicant argues that the treatment of SLE prone mice with a BLys antagonist is proof that the BLys protein can effectively treat a disease condition. The arguments were carefully considered but not found persuasive because once again, the rejection is not towards lack of enablement due to BLys usage. The invention as claimed is treatment of a disease by modulation of NIK-SIVA interaction. Since there is no nexus between this invention and BLys usage the arguments are not persuasive. Also presented in the remarks are the teachings of Novak et al. which demonstrated the effects of BLys in B-CLL. Again the arguments were not persuasive towards enablement because there is no link between BLys and modulation of NIK-SIVA interaction and treatment of a disease.

On page 19 of the Remarks Applicant argues that a series of literature references provide **possible** scenarios as to how the NIK-SIVA complex **could be** linked to a diseases and the **potential of interference** of the interaction to develop treatment strategies. The arguments were carefully considered but not found persuasive because, for instance, the first reference cited (Li-Fan Lu et al.) does not refer to a NIK-SIVA interaction. The only passing reference is by citing the Applicants' work as a possible suggested NIK-SIVA interaction. As such the paper just speculated that it is

possible that in the absence of NIK, SIVA **may not be** recruited to the GITR tail, and **may result** in heightened T cell proliferation. From here Applicant argues that application of an agent that disrupts NIK/SIVA interaction and thereby recruitment of SIVA to the membrane would cause **possible reduction** in apoptosis of T cells and enhanced immune response. The conclusion of the Applicant is that the reference seemingly supports a role/function of NIK as an adaptor to recruit SIVA *apart* from its role in NF-kB activation. This concluding statement however is not persuasive because it is speculative, and lacks the data to support it. The same analysis applied on the other references presented by Applicant lead to the same conclusion: none of the references discuss the interaction of the NIK-SIVA and thus they cannot be supportive of a role of this putative interaction in affecting the outcome of an immune disease.

On page 21 of the Remarks Applicant argues that Matsutomo et al. demonstrates that high levels of SIVA decreases NIK level and function and Gudi et al. SIVA1 negatively regulates NF kappa B activity and this constitutes a rationale for their claim regarding the modulation of NIK_SIVA interaction and its use in treatment of diseases. The arguments were carefully considered but not found persuasive because, again there is no nexus between NIK-SIVA interaction and a disease. The evidence presented by Applicant on pages 22-24 (the papers of Hu et al., Lin et al. , Everett et al. Singh et al.) do not address the heart of the claims, the implication of the NIK_SIVA interaction and of its modulation in treating a disease.

On page 25 of the Remarks Applicant argues that the predictability of in vivo methods for successfully delivering agents that would modulate the interaction between two intracellular proteins is not low since the works of Shibata et al. and Dai et al. show that inhibiting an intracellular protein by external administration of a binding peptide is feasible. The arguments were carefully considered but not found persuasive because they do not address the NIK-SIVA interaction and the effects of its modulation on any disease. The point that needs to be considered is if a modulator can be used (be it a peptide inhibitor), especially in the case that the putative interaction is not established in the literature or working examples are not revealed.

Conclusion

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ELLY-GERALD STOICA whose telephone number is

(571)272-9941. The examiner can normally be reached on 9:00-18:30 M-Th and 9:00-18:30 alternate F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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